AMENDMENT

Amendment to the Specification:

At page 1, line 2, please insert the following paragraphs:

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a national phase application under 35 U.S.C. § 371 of International Application No. PCT/EP2004/004255 filed 22 April 2004, which claims priority to European Application No. 03450097.5 filed 22 April 2003. The entire text of each of the above-referenced disclosures is specifically incorporated herein by reference without disclaimer.

INCORPORATION BY REFERENCE OF SEQUENCE LISTING SUBMITTED ON A COMPACT DISC

The Sequence Listing is submitted on one compact disc (Copy 1), together with a duplicate thereof (Copy 2), each created on October 20, 2005, and each containing one 896 kb file entitled "SONN079US.APP.TXT." The material contained on the compact disc is specifically incorporated herein by reference.

At page 3, please replace the 4th paragraph with the following substitute paragraph:

Three major types of human sera were collected for this purpose. First, healthy adults below <45 years of age were tested for *H. pylori*-specific IgG and IgA serum antibody levels by ELISA using total bacterial lysate and culture supernatant proteins. High titer individuals were interviewed and ~~seleted~~ selected based on the absence of medical history, symptoms or complains related to *H. pylori* diseases. Based on correlative data, protective (colonization neutralizing) antibodies are likely to be present in exposed individuals who are not carriers of *H. pylori* or not susceptible to disease ~~casued~~ caused by *H. pylori*. High titer sera from symptom-free healthy adults were included in the genomic based antigen identification. This approach for selection of human sera is basically very different from that used for *S. aureus*, where carriage or noncarriage state cannot be associated with antibody levels.

At page 3, please replace the last paragraph, spanning pages 3-4, with the following substitute paragraph:

The genomes of the two bacterial species *H. pylori* and *S. aureus* by itself show a number of important differences. The genome of *H. pylori* contains approximately 1.65 Mb sequence information, while *S. aureus* ~~harbours~~ harbors about 2.85 Mb. They have an average GC content of 39 and 33%, respectively. In addition, the two bacterial species require different growth conditions and media for propagation. While *H. pylori* is a strictly human pathogen, *S. aureus* can also be found infecting a range of warm-blooded animals. A list of the most important diseases, which can be inflicted by the two pathogens, is presented below. *S. aureus* causes mainly nosocomial, opportunistic infections: impetigo, folliculitis, abscesses, boils, infected lacerations, endocarditis, meningitis, septic arthritis, pneumonia, osteomyelitis, scalded skin syndrome (SSS), toxic shock syndrome. *H. pylori* causes likely community ~~aquired~~ acquired gastro-intestinal infections: self limiting traveler's diarrhea, corpus predominant or pangastritis, peptic ulcer disease (stomach and duodenum), gastric cancer (adenocarcinoma), chronic atrophic gastritis (CAG) and MALT (mucosa-associated lymphoid tissue, non-Hodgkin's type B cell lymphoma).

At page 11, please replace the 5th paragraph with the following substitute paragraph:

In a preferred embodiment the pharmaceutical composition further comprises an immunostimulatory substance, preferably selected from the group comprising polycationic polymers, especially polycationic peptides, immunostimulatory deoxynucleotides (ODNs), peptides containing at least two LysLeuLys motifs, especially ~~KLKL5KLK~~ $KLKL_5KLK$ (SEQ ID NO:358), neuroactive compounds, especially human growth hormone, ~~alumn~~ alum, Freund's complete or incomplete adjuvants or combinations thereof.

At page 12, please replace the 8th paragraph with the following substitute paragraph:

Moreover, the present invention ~~provids~~ provides a method for producing an antibody according to the present invention, characterized by the following steps:

At page 13, please replace the last paragraph, spanning pages 13-14, with the following substitute paragraph:

The present invention advantageously provides an efficient, relevant and comprehensive set of isolated nucleic acid molecules and their encoded hyperimmune serum reactive antigens or fragments thereof identified from *H. pylori* using an antibody preparation from multiple human plasma pools and surface expression libraries derived from the genome of *H. pylori*. Thus, the present invention ~~fulfils~~ fulfills a widely felt demand for *H. pylori* antigens, vaccines, diagnostics and products useful in procedures for preparing antibodies and for identifying compounds effective against *H. pylori* infection.

At page 16, please replace the 2nd paragraph with the following substitute paragraph:

It is not clear as to what ~~extend~~ extent host ~~defence~~ defense against *H. pylori* relies on innate or adaptive immunological mechanisms. The mucous membranes and the gastric acidic environment are formidable barriers against invasion by Helicobacter. However, once the mucous membranes are breached the first line of non-adaptive cellular ~~defence~~ defense begins its co-ordinate action through complement and phagocytes, especially the polymorphonuclear leukocytes (PMNs) as indicated by the massive neutrophil infiltration of the gastric mucosa in response to the presence of *H. pylori*. Attachment of *H. pylori* induces strong pro-inflammatory cytokine release, including TNF-α, IL-1β and IL-8 that can mediate a local chemoattractant effect for immuno-effector cells, such as granulocytes {Prinz, C. et al., 2003}; {Sutton, P., 2001}. These cells can be regarded as the cornerstones in eliminating invading bacteria. As *H. pylori* is thought to be a exclusively extracellular pathogen, the major anti-Helicobacter adaptive response should come from the humoral arm of the immune system, and this seems to be in agreement with the high titers of primarily IgG and IgA antibodies that develop in patient upon *H. pylori* infection {Prinz, C. et al., 2003}; {Sutton, P., 2001}. The induction of high titer IgG and ~~secretory~~ secretory IgA type antibody response may reflect the importance of adaptive mechanisms in the immune response against this organism. In principle, the effect of these antibodies is mediated through three major mechanisms: promotion of opsonization, toxin neutralisation, and inhibition of adherence. It is believed that opsonization is especially important, because of its requirement for an effective phagocytosis. For efficient opsonization the microbial surface has to be coated with antibodies and complement factors for recognition by PMNs through receptors for the Fc

fragment of IgG molecules or for activated C3b. After opsonization, the bacteria are phagocytosed and killed. Antibodies bound to specific antigens on the cell surface of bacteria serve as ligands for the attachment to PMNs and to promote phagocytosis. The very same antibodies bound to the adhesins and other cell surface proteins are expected to neutralize adhesion and prevent colonization.

At page 19, please replace the 1st paragraph with the following substitute paragraph:

Finally, the nucleic acid molecule according to the present invention can as a fifth alternative also be a nucleic acid molecule which, but for the degeneracy of the genetic code, would hybridise to any of the nucleic acid molecules according to any nucleic acid molecule of the present invention according to the first, second, third, and fourth alternative as outlined above. This kind of nucleic acid molecule refers to the fact that preferably the nucleic acids according to the present invention code for the hyperimmune serum reactive antigens or fragments thereof according to the present invention. This kind of nucleic acid molecule is particularly useful in the detection of a nucleic acid molecule according to the present invention and thus the diagnosis of the respective microorganisms such as *H. pylori* and any disease or diseased condition where this kind of ~~microorganim~~ microorganism is involved. Preferably, the hybridisation would occur or be preformed under stringent conditions as described in connection with the fourth alternative described above.

At page 35, please replace the last paragraph with the following substitute paragraph:

Spiegelmers and their generation or manufacture is based on a similar principle. The manufacture of spiegelmers is described in international patent application WO 98/08856. Spiegelmers are L-nucleic acids, which means that they are composed of L-nucleotides rather than D-nucleotides as aptamers are. Spiegelmers are characterized by the fact that they have a very high stability in biological systems and, comparable to aptamers, specifically interact with the target molecule against which they are directed. In the process of generating spiegelmers, a ~~heterogeenous~~ heterogenous population of D-nucleic acids is created and this population is contacted with the optical antipode of the target molecule, in the present case for example with the D-enantiomer of the naturally occurring L-enantiomer of the hyperimmune serum reactive antigens and fragments thereof according to the present

invention. Subsequently, those D-nucleic acids are separated which do not interact with the optical antipode of the target molecule. But those D-nucleic acids interacting with the optical antipode of the target molecule are separated, optionally identified and/or sequenced and subsequently the corresponding L-nucleic acids are synthesized based on the nucleic acid sequence information obtained from the D-nucleic acids. These L-nucleic acids which are identical in terms of sequence with the aforementioned D-nucleic acids interacting with the optical antipode of the target molecule, will specifically interact with the naturally occurring target molecule rather than with the optical antipode thereof. Similar to the method for the generation of aptamers it is also possible to repeat the various steps several times and thus to enrich those nucleic acids specifically interacting with the optical antipode of the target molecule.

At page 38, please replace the 3rd paragraph with the following substitute paragraph:

The present invention also includes a vaccine formulation, which comprises the immunogenic recombinant protein together with a suitable carrier. Since the protein may be broken down in the stomach, it is preferably administered parenterally, including, for example, administration that is subcutaneous, intramuscular, intravenous, intradermal intranasal or ~~tramsdermal~~ transdermal. Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the bodily fluid, preferably the blood, of the individual; and aqueous and non-aqueous sterile suspensions which may include suspending agents or thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example, sealed ampoules and vials, and may be stored in a freeze-dried condition requiring only the addition of the sterile liquid carrier immediately prior to use. The vaccine formulation may also include adjuvant systems for enhancing the immunogenicity of the formulation, such as oil-in-water systems and other systems known in the art. The dosage will depend on the specific activity of the vaccine and can be readily determined by routine experimentation.

At page 39, please replace the 2nd paragraph with the following substitute paragraph:

It is also within the scope of the present invention that the pharmaceutical composition,

especially vaccine, comprises apart from the hyperimmune serum reactive antigens, fragments thereof and/or coding nucleic acid molecules thereof according to the present invention other compounds which are biologically or pharmaceutically active. Preferably, the vaccine composition comprises at least one polycationic peptide. The polycationic compound(s) to be used according to the present invention may be any polycationic compound, which shows the characteristic effects according to the WO 97/30721. Preferred polycationic compounds are selected from basic ~~polyppetides~~ polypeptides, organic polycations, basic polyamino acids or mixtures thereof. These polyamino acids should have a chain length of at least 4 amino acid residues (WO 97/30721). Especially preferred are substances like polylysine, polyarginine and polypeptides containing more than 20 %, especially more than 50 % of basic amino acids in a range of more than 8, especially more than 20, amino acid residues or mixtures thereof. Other preferred polycations and their pharmaceutical compositions are described in WO 97/30721 (e.g. polyethyleneimine) and WO 99/38528. Preferably these polypeptides contain between 20 and 500 amino acid residues, especially between 30 and 200 residues.

At page 39, please replace the last paragraph, spanning pages 39-40, with the following substitute paragraph:

Polycationic compounds derived from natural sources include HIV-REV or HIV-TAT (derived cationic peptides, antennapedia peptides, chitosan or other derivatives of chitin) or other peptides derived from these peptides or proteins by biochemical or recombinant production. Other preferred polycationic compounds are cathelin or related or derived substances from cathelin. For example, mouse cathelin is a peptide, which has the amino acid sequence NH_2-~~RLAGLLRKGGEKIGEKLKKIGQKIKNFFQKLVPQPE-COOH~~ RLAGLLRKGGEKIGEKLKKIGQKIKNFFQKLVPQPE-COOH (SEQ ID NO:357). Related or derived cathelin substances contain the whole or parts of the cathelin sequence with at least 15-20 amino acid residues. Derivations may include the substitution or modification of the natural amino acids by amino acids, which are not among the 20 standard amino acids. Moreover, further cationic residues may be introduced into such cathelin molecules. These cathelin molecules are preferred to be combined with the antigen. These cathelin molecules surprisingly have turned out to be also effective as an adjuvant for an antigen without the addition of further adjuvants. It is therefore possible to use such cathelin molecules as efficient adjuvants in vaccine formulations with or without further immunactivating substances.

At page 40, please replace the 2nd paragraph with the following substitute paragraph:

The pharmaceutical composition of the present invention may further comprise immunostimulatory nucleic acid(s). Immunostimulatory nucleic acids are e. g. neutral or artificial CpG containing nucleic acids, short stretches of nucleic acids derived from non-vertebrates or in form of short oligonucleotides (ODNs) containing non-methylated cytosine-guanine di-nucleotides (CpG) in a certain base context (e.g. described in WO 96/02555). Alternatively, also nucleic acids based on inosine and cytidine as e.g. described in the WO 01/93903, or deoxynucleic acids containing deoxy-inosine and/or deoxyuridine residues (described in WO 01/93905 and PCT/EP 02/05448, incorporated herein by reference) may preferably be used as immunostimulatory nucleic acids for the present invention. ~~Preferablly~~ Preferably, the mixtures of different immunostimulatory nucleic acids may be used according to the present invention.

At page 41, please replace the 8th paragraph with the following substitute paragraph:

In connection with the present invention any disease related use as disclosed herein such as, e.g. use of the pharmaceutical composition or vaccine, is particularly a disease or diseased condition which is caused by, linked or associated with Helicobacter, more preferably, *H. pylori*. In connection therewith it is to be noted that *H. pylori* comprises several strains including those disclosed herein. A disease related, caused or associated with the bacterial infection to be prevented and/or treated according to the present invention includes besides others peptic ulcer and ~~assoziated~~ associated cancer in humans.

At page 42, please replace the 4th paragraph with the following substitute paragraph:

Potential antagonists include small organic molecules, peptides, polypeptides and antibodies that bind to a hyperimmune serum reactive antigen and fragments thereof of the invention and thereby inhibit or extinguish its ~~acitivity~~ activity. Potential antagonists also may be small organic molecules, a peptide, a polypeptide such as a closely related protein or antibody that binds to the same sites on a binding molecule without inducing functional activity of the hyperimmune serum reactive antigens and fragments thereof of the invention.

At page 44, please replace the 7th paragraph with the following substitute paragraph:

Figure 1 shows the characterization of human sera for anti-*H. pylori* antibodies as measured by immune assays. Total anti- *H. pylori* IgG and IgA antibody levels were measured by standard ELISA using total bacterial lysate prepared from *H. pylori* KTH Ca1 strain as coating antigen. **(A)** Serum samples from randomly selected 54 adults were analysed for antibody levels and afterwards interviewed for symptoms (~~gasctric~~ gastric pain) and previous history of *H. pylori* infections. Four individuals were identified with high antibody titers without symptoms or disease (S-) and four with acute symptoms or known clinical disease (S+). **(B)** Sera from patients presenting themselves with typical symptoms of *H. pylori* diseases were analysed for IgG and IgA levels and grouped based on negative or positive results in the Urease test performed by clinicians. ELISA units are calculated from absorbance readings at two serum dilutions (10.000X and 50.000X). Averages for the two different groups are given. **(C)** Immunoblot analysis was performed on sera pre-selected by ELISA in order to ensure multiple immune reactivity with protein antigens. Results of a representative experiment using total bacterial lysate prepared from *H. pylori* KTH Ca1 strain and selected sera at 5.000X dilution are shown. Serum samples are from; Lane 1: a high titer S- individual, Lane 2: a high titer urease -patient, Lane 3 and 4: a high titer urease + patient. Lane 1-3 was developed with anti-human IgG secondary antibody and Lane 4 with anti-human IgA secondary antibody. Mw: molecular ~~weigth~~ weight markers.

At page 45, please replace the 4th paragraph with the following substitute paragraph:

Table 3: Epitope serology with human sera.
Immune reactivity of individual synthetic peptides representing selected epitopes with individual human sera is shown. Extent of reactivity is colour coded; white: neg (<500), light grey: + (500-650), dark grey: ++ (650-800), and black: +++ (>800). Numbers represent ELISA readings generated by measuring OD_{405nm} at serum dilution 200X. S stands for score, calculated as the sum of all reactivities (addition of the number of all +); P1 to P18 sera are from patients with definitive clinical diagnosis of duodenal or gastric ulcer, N1-4 sera are from healthy adults with high anti-*H. pylori* antibody titers without clinical ~~symptomes~~ symptoms of *H. pylori* disease. Location of synthetic peptides within the antigenic ORFs according to the genome annotation of *H. pylori* strain 26695 are given in columns **from** and **to** indicating the first and last amino acid residues, respectively. Peptide names: HP0009.1

present in annotated ORF HP0009.

At page 46, please replace the last paragraph, spanning pages 46-47, with the following substitute paragraph:

The sera were characterized for anti-*H. pylori* antibodies by a series of ELISA and immunoblotting assays. For that purpose two different antigen preparation were used: whole cell extracts prepared from *H. pylori* strains KTH-Ca1 and KTH-Du and both IgG and IgA antibody levels were determined. Antibody titers were expressed as units calculated from absorbance readings at two different dilutions - 10.000X and 50.000X for IgG and 1.000X and 5.000X for IgA - where the response was linear (Fig 1A and B). Among the high titer randomly taken individuals ~~eigth~~ eight out of the 54 included (15%) showed significant IgG and IgA antibody levels. Half of these individuals were known *H. pylori* 'patients' acutely or before, the other half had no medical history or any complains. Sera of these four individuals were pooled and prepared for antigen identification. Since *H. pylori* infections are common, antibodies are present as a consequence of natural immunization from previous encounters with *Helicobacter* even without consequent carriage. The value of the ELISA assay ~~imployed~~ employed were further proved by analyzing patients' sera with or without active disease. Comparing the antibody levels in urease test positive and urease test negative individuals, significantly higher antibody levels were measured in the Urease + group (Fig. 1B). According to literature data, the false negative cases (~ 10%) are much more prevalent then the false positives in this test, suggesting that the ELIAS assays is likely to be even more powerful predicting active *H. pylori* infections. Sera were ranked based on the reactivity against total lysate preparation in both antibody classes, and the highest ones from all three serum donor groups were selected for further analysis by immunoblotting. This latter assay confirmed immune reactivity against multiple *H. pylori* proteins, as it is ~~examplified~~ exemplified on Fig. 1C.

Please delete the Sequence Listing numbered pages 1-79, and replace it with the Sequence Listing submitted concurrently herewith on compact disc.